Cluster analysis of mortality and malformations in the Provinces of Naples and Caserta (Campania Region)

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Summary. The possible adverse health effects associated with the residence in the neighbourhood of toxic dump sites have been the object of many epidemiological studies in the last two decades; some of these reported increases of various health outcomes. The present study reports the cluster analysis of mortality and malformations at municipality level, standardized by socioeconomic deprivation index, in an area of the Campania Region characterized by a widespread illegal practice of dumping toxic and urban waste. Clusters have been observed with significant excess of mortality by lung, liver, gastric, kidney and bladder cancers and of prevalence of total malformations and malformations of limb, cardiovascular and urogenital system. The clusters are concentrated in a sub-area where most of the illegal practice of dumping toxic waste has taken place.

Key words: cluster, mortality, malformations, toxic waste.

Riassunto *(Analisi dei cluster di mortalità e malformazioni congenite nelle province di Napoli e Caserta, regione Campania)*. I possibili effetti sanitari associati alla residenza in prossimità di siti di smaltimento di rifiuti tossici sono stati oggetto di diverse indagini epidemiologiche, alcune delle quali hanno riportato incrementi di patologie. Il presente studio illustra le analisi dei cluster della mortalità e delle malformazioni congenite a livello comunale, svolte in un'area della Campania caratterizzata da siti di smaltimento illegale di rifiuti tossici e urbani. Sono stati evidenziati cluster con eccessi significativi della mortalità per tumore del polmone, fegato, stomaco, rene e vescica e di prevalenza delle malformazioni congenite totali, degli arti, del sistema cardiovascolare e dell'apparato urogenitale. I cluster sono concentrati in una sub-area a cavallo delle due province nella quale sono più numerosi i siti di smaltimento illegale dei rifiuti tossici.

Parole chiave: cluster, mortalità, malformazioni congenite, rifiuti tossici.

INTRODUCTION

The issue of possible adverse health effects associated with residence in the neighbourhood of toxic waste dump sites has been the object of a number of epidemiological studies performed in different countries in the last two decades; several studies report increased risks of cancer, congenital malformations (CMs) and other diseases, but no causal link has been so far adequately assessed [1-5]. A recent WHO workshop [6] stated that the evidence so far available of health risks in the neighbourhood of waste dumping sites deserves attention even if a causal link has not yet been proven.

A widespread illegal practice of dumping or burning toxic and industrial wastes, as well as solid urban waste, took place since the '80s in an area of Campania Region located North of Naples and South of Caserta (for a recent review, [7]). The awareness of this problem dates back to the mid Nineties prompting some early exploratory studies aimed at estimating:

- its possible health impact [8, 9], and
- some methodological discussion on how to properly investigate such a complex issue [10, 11].

In this frame, in 2004, the Department of Civil Defence of the Italian Government requested the World Health Organization – European Centre for Environment and Health – to conduct an epidemiological study

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on the health impact of the waste cycle in Campania. A working group including WHO, Istituto Superiore di Sanità, National Research Council, Campania Region Epidemiologic Observatory and Environmental Protection Agency was then appointed, and it started to cooperate with local health authorities, cancer and CMs registries and environmental organizations [12]. The first investigation carried out by the working group was a geographic study on cancer mortality and occurrence of CMs in the Provinces of Naples and Caserta. The study, based on standardized mortality ratios (SMR) and Bayesian mortality ratios (BMR) estimated at the municipal level, detected an area located in the southern part of Caserta Province and in the corresponding northern part of Naples Province, characterized by significantly increased cancer mortality and CMs occurrence rates, if compared with Campania Region reference figures [13]. This area corresponds, in qualitative terms, with the area where most illegal dumping of toxic waste took place.

The purpose of the present paper is to further investigate the issue with a cluster analysis approach, in order to evaluate the presence of neighbouring groups of municipalities presenting significant increases of cancer and CMs with respect to the whole study area, also taking into account the possible role of socioeconomic deprivation by use of a deprivation index (DI) estimated for each municipality.

The present study focuses on a set of neoplastic diseases for which some studies report an association with residence in the neighbourhood of toxic dump sites, landfills and incinerators (in view of the widespread use to set fire to waste disposal sites in the study area), and on all the main groups of CMs.

MATERIALS AND METHODS

Demographic data

The study area includes the 195 municipalities of the Provinces of Naples (91) and Caserta (104).

The source of demographic data is the National Bureau of Statistics (ISTAT). Figures are available for each municipality and are specific for age class, gender and year for the time-window 1994-2002. Denominators of mortality rates are based on the sum of annual residential populations (age: 0-85+) for the considered study period (1994-2001).

Municipalities are the smallest administrative units (8100 in all of Italy) for which mortality data are routinely available. Naples, alone, accounts for 33% of the population of the Naples Province, and thus was removed from the analysis in order to prevent the loss of information provided by all the other municipalities. Among the latter, size ranges from a minimum of 561 (Rocchetta e Croce) to a maximum of 96 912 (Torre del Greco) inhabitants.

Denominators of CMs rates are constituted by live births resident in each municipality at study over the period 1996-2002. The total births in the study period were 351 516 (50 217 annual average), with 4192 registered congenital malformations.

Socioeconomic deprivation

In environmental epidemiology socioeconomic deprivation indexes are aimed at taking into account possible confounding due to an unfavourable socioeconomic situation of the populations resident in polluted sites. The point was raised by authors investigating the issue of environmental equity [14]. Previous epidemiological investigation on areas at environmental risk in Italy [15] used the deprivation index (DI) constructed by Cadum [16], which refers to the British experience [17, 18]. The DI is based on a factorial analysis that selected five socioeconomic variables measured in the 1991 Population Census showing the strongest association with mortality:

- proportion of population with only primary education;
- proportion of unemployed among active population;
- proportion of population not owning its dwelling;
- proportion of monoparental families;
- average surface of dwellings.

In the present study, the five variables of interest have been standardized with respect to the mean value and standard deviation of their distribution in the Provinces of Naples and Caserta. The algebraic sum of the five standardized variables (mean surface of dwellings taken with negative sign) provides DI as a continuous variable. Each municipality has thus a single DI value, ranging from negative to positive value, corresponding to increasing levels of social impairment. The index has then been categorized in quintiles, and thus used in the cluster analysis. The index is based on figures from 1991 Population Census. Data from 2001 were also available, but they were regarded as being too close in time to the end of the study period (2001 for mortality, 2002 for CMs). A good correlation ($r = 0.85$) was observed between the 1991 and 2001 versions of DI, thus showing that in practical terms their use is almost equivalent.

Health data

The source of mortality data is ISTAT. The following causes of death were investigated:

- Malignant neoplasms of
  - trachea, bronchus and lung (ICD IX Revision code 162);
  - liver (ICD IX Revision code 155.0-155.1, 156);
  - stomach (ICD IX Revision code 151);
  - bladder (ICD IX Revision code 188);
  - kidney (ICD IX Revision code 189);
  - connective tissue excluding the bone (ICD IX Revision code 171).
- Non-Hodgkin's lymphoma (ICD IX Revision code 200, 202).

Non-Hodgkin's lymphoma and soft tissue sarcomas (these latter resulting from ICD code 171) were included because dioxin has been suggested as an etiologic factor, and this agent can be produced by combustion of both urban and industrial wastes. As discussed later, the use of mortality as an indicator

of the occurrence of these neoplasms is not entirely satisfactory. They have been included, though, because any major departure of observed from expected figures would have pointed to an underlying actual increase in incidence.

The source of data on CMs is the Campania Region Registry of Birth Defects with reference to the Provinces of Naples and Caserta, 1996-2002. The CMs object of the present study, with the corresponding ICD IX and ICD X codes (WHO, 1992-1994) are listed in *Table 1*. The case list includes:

- induced abortions subsequent to prenatal diagnoses of CMs through 24th week of pregnancy;
- fetal deaths since 20th week of pregnancy;
- live births for which CMs were ascertained both at birth or in the postnatal period.

Cluster analysis usually investigates spatial aggregation of individual cases. In geographic mortality studies based on municipality data, like the present one, clusters are defined as sums of cases resident in neighbouring municipalities significantly exceeding expected figures. The latter are computed by indirect standardization using mortality rates of the population resident in the Provinces of Naples and Caserta, with the exclusion of Naples (for the reasons described above).

Cluster analysis was performed according to the procedure Spatial Scan Statistics [19]. The number of cases in each municipality is assumed to follow a Poisson distribution. The procedure employs a circular window of varying radius that moves on the whole study area. The window is centred at each step on one of the municipalities, identified by the x, y coordinates of its townhall. The radius is calculated as the distance between the different townhalls; it varies from 0 (whenever a single municipality is included in the cluster) to a fixed maximum (10 km). The procedure identifies for each municipality the circular area with the maximum excess of cases (maximum value of standardized mortality/morbidity ratio) and selects all those showing significant departures from expected values based on likelyhood ratio test (LRT). Significance levels were fixed at $p < 0.05$ (LRT > 7.16).

Both cluster analyses (mortality and CMs) were standardized for DI; mortality analyses were also age standardized and performed both separately for each gender and in the overall population.

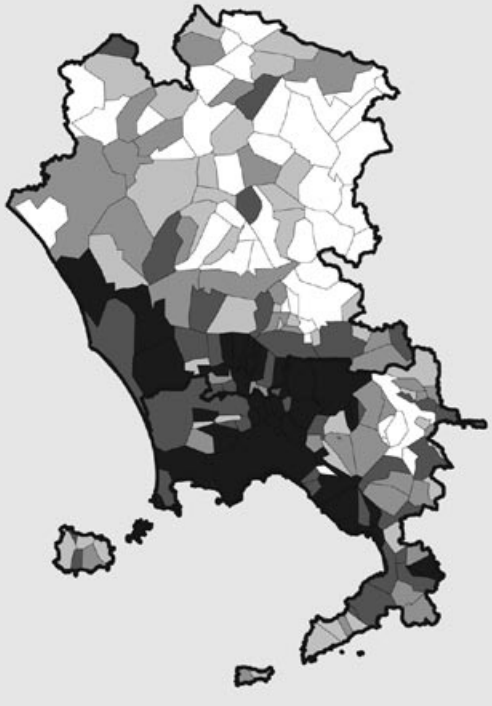
RESULTS

Socioeconomic deprivation

The map shows the distribution of municipality values of DI, calculated as described before, in the study area.

The municipalities of the Provinces of Naples and Caserta were subdivided in quintiles with respect to the value of the deprivation index (the first represents the most wealthy, the fifth the most deprivated). The most wealthy municipalities result in the north-eastern part of Caserta Province, and the most deprivated in the northern part of the Naples Province and in the southern and western parts of Caserta Province *(Figure 1)*.

The present cluster analysis is adjusted by DI.



V quintile (40 municipalities): Acerra, Afragola, Arzano, Aversa, Boscotrecase, Brusciano, Caivano, Cancello ed Arnone, Carinaro, Casaluce, Casandrino, Casapesenna, Casavatore, Casola di Napoli, Casoria, Castello di Cisterna, Cercola, Crispano, Ercolano, Frattamaggiore, Frignano, Gricignano di Aversa, Grumo Nevano, Lettere, Marano di Napoli, Massa di Somma, Melito di Napoli, Mondragone, Monte di Procida, Napoli, Orta di Atella, Pozzuoli, Procida, Qualiano, San Marcellino, Sant'Antimo, Teverola, Torre Annunziata, Torre del Greco, Villa Literno.

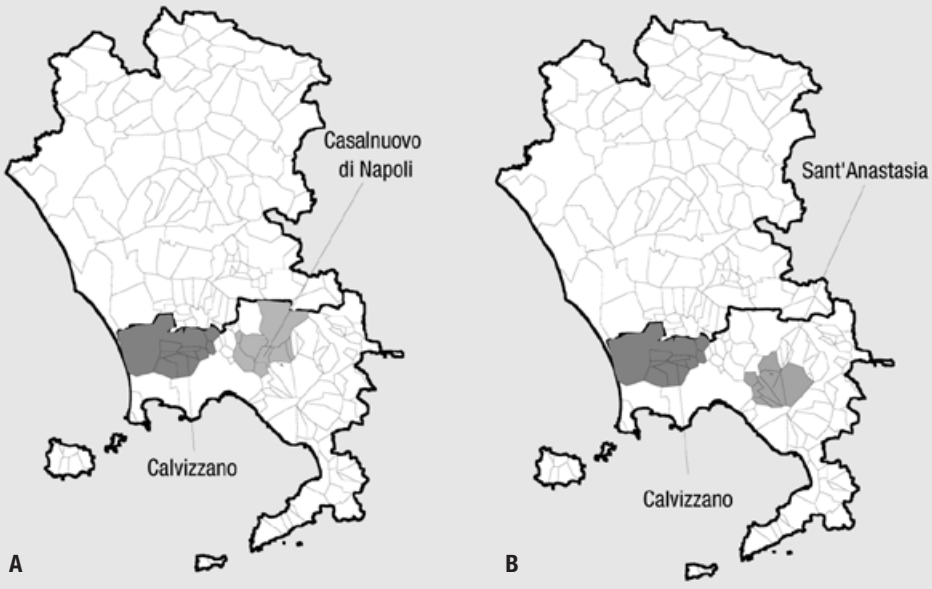
IV quintile (39 municipalities): Arienzo, Bacoli, Boscoreale, Calvizzano, Cardito, Casal di Principe, Casalnuovo di Napoli, Casamarciano, Castellammare di Stabia, Castel Volturno, Cimitile, Formicola, Francolise, Frattaminore, Giugliano in Campania, Gragnano, Lacco Ameno, Lusciano, Maddaloni, Marcianise, Mariglianella, Meta, Mugnano di Napoli, Ottaviano, Palma Campania, Parete, Portici, Raviscanina, San Giorgio a Cremano, San Pietro Infine, Santa Maria Capua Vetere, Santa Maria la Carità, Santa Maria la Fossa, Serrara Fontana, Succivo, Trecase, Vico Equense, Villa di Briano, Visciano.

III quintile (39 municipalities): Agerola, Ailano, Anacapri, Barano d'Ischia, Capodrise, Capua, Carinola, Cesa, Cicciano, Ciorlano, Comiziano, Conca della Campania, Grazzanise, Liveri, Macerata Campania, Marigliano, Marzano Appio, Pimonte, Poggiomarino, Quarto, Roccamonfina, Roccaromana, San Felice a Cancello, San Giuseppe Vesuviano, San Gregorio Matese, San Prisco, Sant'Agnello, Santa Maria a Vico, Sant'Anastasia, Sant'Antonio Abate, Sant'Arpino, San Vitaliano, Sessa Aurunca, Somma Vesuviana, Sparanise, Terzigno, Trentola-Ducenta, Tufino, Volla.

II quintile (39 municipalities): Cavi Risorta, Camposano, Capri, Capriati a Volturno, Carbonara di Nola, Casamicciola Terme, Castel di Sasso, Cervino, Curti, Dragoni, Falciano del Massico, Forio, Ischia, Letino, Liberi, Massa Lubrense, Mignano Monte Lungo, Pastorano, Piano di Sorrento, Pietravairano, Pollena Trocchia, Pomigliano d'Arco, Pompei, Portico di Caserta, Presenzano, Recale, Riardo, Roccarainola, Rocchetta e Croce, San Cipriano d'Aversa, San Marco Evangelista, San Paolo Bel Sito, San Tammaro, Sorrento, Striano, Teano, Valle Agricola, Valle di Maddaloni, Villaricca.

I quintile remaining 39 municipalities.

Fig. 1 | *Municipality distribution of DI values subdivided in quintiles.*



A

Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Calvizzano	9	5.56	1008	793.5	1.30	0.0003
2	Casalnuovo di Napoli	8	5.45	1002	884.0	1.15	0.03

Cluster n.	Municipalities included (number of cases)
1	Calvizzano (47), Marano di Napoli (182), Mugnano di Napoli (102), Villaricca (78), Giugliano in Campania (255), Qualiano (53), Melito di Napoli (80), Quarto (103), Sant'Antimo (108)
2	Casalnuovo di Napoli (98), Afragola (214), Pomigliano d'Arco (158), Acerra (124), Volla (68), Casoria (259), Castello di Cisterna (24), Cardito (57)

B

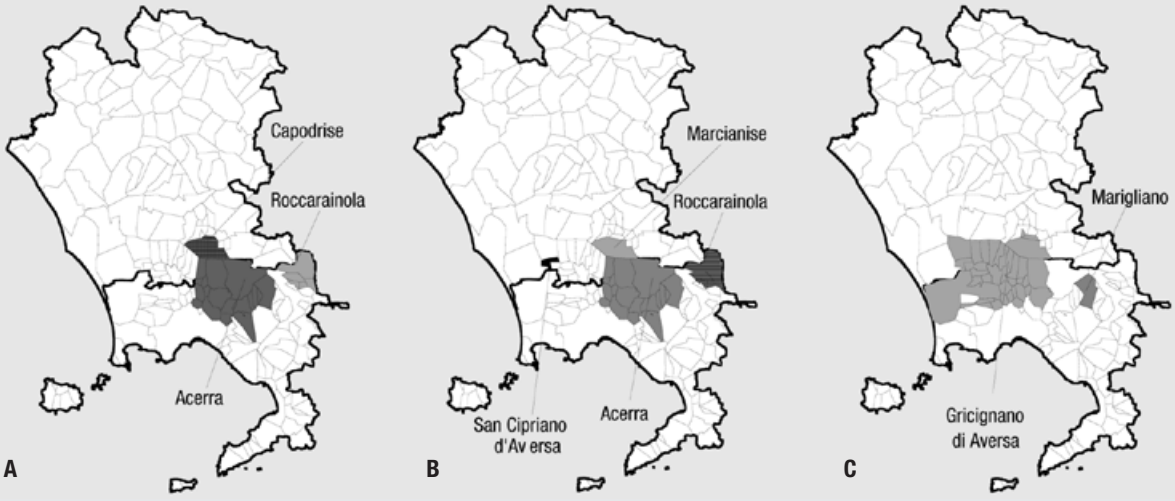
Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Calvizzano	9	5.56	876	687.8	1.31	0.0003
2	Sant'Anastasia	8	5.09	496	412.2	1.22	0.0203

Cluster n.	Municipalities included (number of cases)
1	Calvizzano (43), Marano di Napoli (159), Mugnano di Napoli (95), Villaricca (65), Giugliano in Campania (218), Qualiano (44), Melito di Napoli (69), Quarto (88), Sant'Antimo (95)
2	Sant'Anastasia (87), Pollena Trocchia (34), Somma Vesuviana (96), Massa di Somma (5), Cercola (50), San Sebastiano al Vesuvio (25), Pomigliano d'Arco (139), Volla (60)

Fig. 2 | *Lung cancer mortality (A: total population; B: males only).*

Mortality

Two clusters of lung cancer in the total population were identified in central part of the Province of Naples *(Figure 2A)*. When considering only the male population, two clusters were detected as well *(Figure 2B)*. One cluster belongs to both maps, while a further cluster appears at the slopes of Vesuvium volcano, in the southern part of Naples Province. Three clusters of liver cancer were detected in the total population: two of them in the northern part of the Province of Naples and one in the neighbouring southern part of the Province of Caserta *(Figure 3A)*. The overall pattern is largely determined by male mortality, which shows a further cluster based on one municipality at



A

Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Acerra	18	9.37	665	505.3	1.40	0.0003
2	Capodrise	2	1.03	91	45.3	2.04	0.0003
3	Roccarainola	5	3.22	58	30.4	1.93	0.0090

Cluster n.	Municipalities included (number of cases)
1	Acerra (36), Casalnuovo di Napoli (32), Pomigliano d'Arco (42), Castello di Cisterna (12), Brusciano (22), Mariglianella (8), Afragola (85), Caivano (59), Cardito (34), Crispano (7), Marigliano (73), Volla (20), Casoria (79), Frattaminore (19), Frattamaggiore (56), Sant'Anastasia (25), Orta di Atella (12), Arzano (46)
2	Capodrise (12), Marcianise (79)
3	Roccarainola (16), Tufino (8), Cicciano (21), Comiziano (1), Camposano (12)

B

Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Acerra	18	9.37	417	285.7	1.61	0.0003
2	Marcianise	1	-	53	22.0	2.46	0.0003
3	San Cipriano d'Aversa	1	-	18	5.4	3.34	0.0160
4	Roccarainola	5	3.22	35	16.7	2.12	0.0463

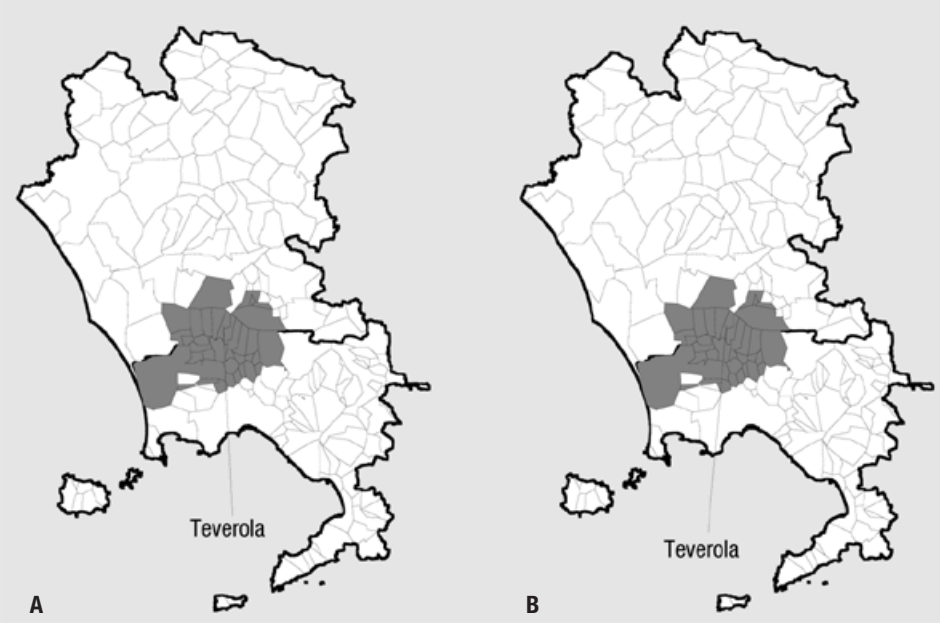
Cluster n.	Municipalities included (number of cases)
1	Acerra (23), Casalnuovo di Napoli (22), Pomigliano d'Arco (32), Castello di Cisterna (7), Brusciano (14), Mariglianella (5), Afragola (47), Caivano (38), Cardito (27), Crispano (5), Marigliano (38), Volla (8), Casoria (44), Frattaminore (14), Frattamaggiore (35), Sant'Anastasia (17), Orta di Atella (7), Arzano (34)
2	Marcianise (53)
3	San Cipriano d'Aversa (18)
4	Roccarainola (8), Tufino (4), Cicciano (13), Comiziano (0), Camposanto (10)

C

Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Marigliano	1	-	35	15.9	2.23	0.0123
2	Gricignano di Aversa	36	9.23	351	295.0	1.26	0.0880

Cluster n.	Municipalities included (number of cases)
1	Marigliano (35)
2	Gricignano di Aversa (2), Carinaro (1), Cesa (3), Teverola (3), Succivo (1), Aversa (34), Sant'Arpino (9), Casaluce (2), Orta di Atella (5), Lusciano (7), Sant'Antimo (12), Frattaminore (5), Trentola-Ducenta (10), San Marcellino (9), Frignano (5), Casandrino (4), Grumo Nevano (6), Crispano (2), Frattamaggiore (21), Villa di Briano (1), Parete (5), Giugliano in Campania (50), Caivano (21), Melito di Napoli (2), Cardito (7), Villaricca (4), Marcianise (26), Casapesenna (2), Mugnano di Napoli (9), Arzano (12), San Cipriano d'Aversa (4), Capodrise (9), Casal di Principe (13), Calvizzano (6), Afragola (36), Portico di Caserta (3)

Fig. 3 | *Liver cancer mortality (A: total population; B: males only; C: females only).*



A

Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Teverola	35	9.54	615	489.8	1.33	0.0003

Cluster n.	Municipalities included (number of cases)
1	Teverola (8), Casaluce (7), Carinaro (6), Aversa (54), Gricignano di Aversa (3), Frignano (10), San Marcellino (14), Lusciano (14), Trentola-Ducenta (14), Villa di Briano (4), Cesa (13), Succivo (10), Parete (4), Sant'Arpino (3), Orta di Atella (12), Sant'Antimo (30), Casapesenna (5), San Cipriano d'Aversa (15), Casal di principe (28), Frattaminore (12), Giugliano in Campania (63), Casandrino (6), Grumo Nevano (20), Crispano (3), Frattamaggiore (45), Villaricca (17), Melito di Napoli (22), Marcianise (52), Caivano (7), Portico di Caserta (10), San Tammaro (9), Cardito (14), Capodrise (6), Mugnano di Napoli (31), Macerata Campania (17)

B

Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Teverola	35	9.54	383	308.3	1.31	0.0050

Cluster n.	Municipalities included (number of cases)
1	Teverola (5), Casaluce (4), Carinaro (4), Aversa (34), Gricignano di Aversa (3), Frignano (5), San Marcellino (6), Lusciano (9), Trentola-Ducenta (8), Villa di Briano (2), Cesa (12), Succivo (9), Parete (4), Sant'Arpino (3), Orta di Atella (9), Sant'Antimo (21), Casapesenna (4), San Cipriano d'Aversa (9), Casal di Principe (18), Frattaminore (6), Giugliano in Campania (40), Casandrino (6), Grumonevano (12), Crispano (3), Frattamaggiore (22), Villaricca (8), Melito di Napoli (14), Marcianise (33), Caivano (21), Portico di Caserta (3), San Tammaro (6), Cardito (8), Capodrise (4), Mugnano di Napoli (19), Macerata Campania (9)

Fig. 4 | *Gastric cancer mortality (A: total population; B: males only).*

the border between Naples and Caserta Provinces *(Figure 3B)*. Liver cancer in women shows a big cluster around the border of the Provinces, and a smaller cluster in the Province of Naples based on one municipality *(Figure 3C)*.

Gastric cancer shows one big cluster in the north-western part of Naples and south-western part of Caserta Province, on both sides of the border *(Figure 4A)*. Male mortality determines the shape of the cluster *(Figure 4B)*.

Bladder cancer mortality determines two clusters in the total population *(Figure 5A)*, one located in the north-western part of Naples Province (essentially explained by male mortality, *Figure 5B*) and one located in the south-eastern part of Caserta Province.

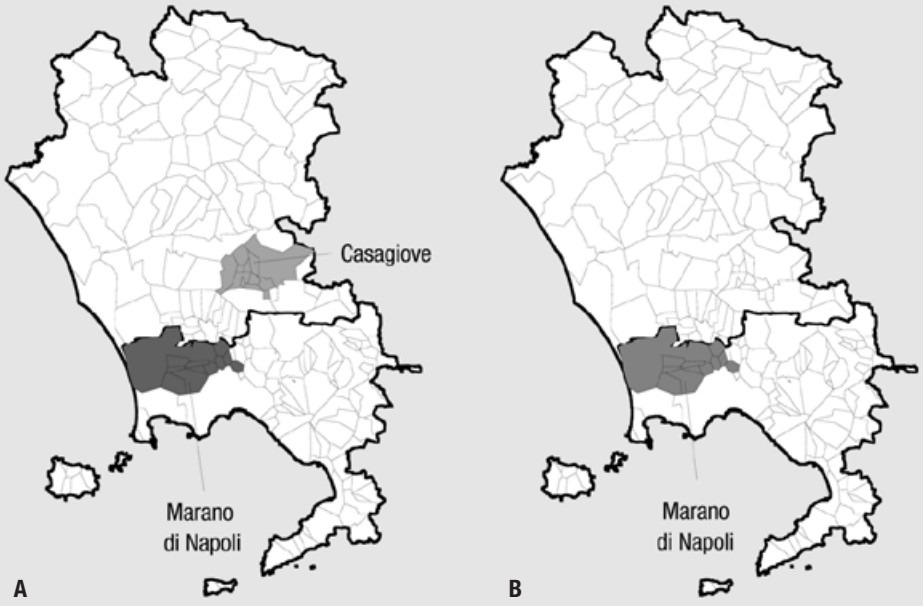
Kidney cancer shows one cluster in the total population, located in the north-western part of Naples Province *(Figure 6)*.

Finally, no clustering of soft-tissue sarcoma and Non-Hodgkin's lymphoma was detected.

Malformations

Five clusters of total CMs were detected *(Figure 7)*, one represented by a single municipality. The major cluster, whose centroid is in the Pomigliano d'Arco municipality, is located in the north-eastern part of the Province of Naples and it extends south towards the Vesuvium volcano. Other two clusters are located in the southern part of the Provinces being investigated.

Two clusters of cardiovascular defects were observed in the Province of Naples *(Figure 8)*, one partly overlapping the major cluster of total CMs.



A

Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Marano di Napoli	11	6.93	206	149.0	1.44	0.0040
2	Casagiove	11	4.36	161	114.2	1.45	0.0143

Cluster n.	Municipalities included (number of cases)
1	Marano di Napoli (37), Calvizzano (12), Mugnano di Napoli (18), Villaricca (10), Giugliano in Campania (46), Qualiano (9), Quarto (18), Melito di Napoli (12), Sant'Antimo (15), Casandrino (6), Arzano (23)
2	Casagiove (6), Casapulla (7), Caserta (59), Curti (5), Recale (6), San Prisco (5), Macerata Campania (10), Portico di Caserta (4), San Nicola la Strada (15), Capodrise (5), Santa Maria Capua Vetere (39)

B

Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Marano di Napoli	11	6.93	174	127.4	1.42	0.0207

Cluster n.	Municipalities included (number of cases)
1	Marano di Napoli (31), Calvizzano (8), Mugnano di Napoli (17), Villaricca (9), Giugliano in Campania (38), Qualiano (8), Quarto (16), Melito di Napoli (9), Sant'Antimo (13), Casandrino (6), Arzano (19)

Fig. 5 | *Bladder cancer mortality (A: total population; B: males only).*

Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Giugliano in Campania	9	4.45	82	51.0	1.70	0.0157

Cluster n.	Municipalities included (number of cases)
1	Giugliano in Campania (21), Villaricca (3), Mugnano di Napoli (11), Melito di Napoli (5), Calvizzano (2), Sant'Antimo (9), Casandrino (8),Marano di Napoli (19), Cesa (4)

Fig. 6 | *Kidney cancer mortality (total population).*

Three clusters of urogenital tract anomalies were identified in the south of Caserta and north of Naples Provinces, the latter partly overlapping the clusters observed for total CMs *(Figure 9)*.

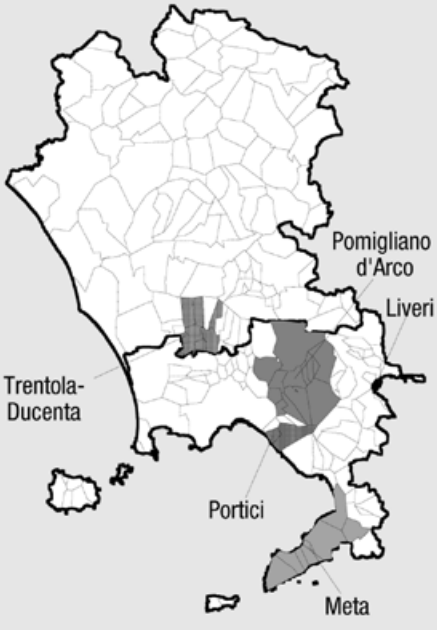
A cluster of limb malformations is located in a large area of the Province of Naples *(Figure 10)*.

No other category of CMs shows any significant clustering.

DISCUSSION

In order to critically evaluate the findings of the present study, it seems appropriate to firstly examine the issue of data quality.

Mortality data in Italy are largely used in epidemiology, and the specific issues associated with their use in geographic studies on environmental health have been recently addressed in the frame of epide-



Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Pomigliano D'arco	13	6.82	561	437.5	1.28	0.0001
2	Meta	8	8.92	216	146.8	1.47	0.0001
3	Trentola Ducenta	8	3.35	194	136.7	1.42	0.0016
4	Portici	2	1.23	157	111.4	1.41	0.0130
5	Liveri	1	-	9	1.5	5.85	0.0159

Cluster n.	Municipalities included (number of cases)
1	Pomigliano D'arco (43), Castello Di Cisterna (5), Casalnuovo Di Napoli (82), Brusciano (18), Acerra (89), Mariglianella (10), Sant'anastasia (33), Volla (40), Somma Vesuviana (42), Marigliano (42), Pollena Trocchia (20), Cercola (25), Afragola (112)
2	Meta (5), Piano Di Sorrento (13), Sant'agnello (4), Vico Equense (23), Sorrento (19), Massa Lubrense (20), Pimonte (11), Castellammare Di Stabia (121)
3	Trentola Ducenta (27), San Marcellino (21), Lusciano (12), Aversa (85), Parete (15), Frignano (9), Villa Di Briano (11), Teverola (14)
4	Portici (69), Ercolano (88)
5	Liveri (9)

Fig. 7 | *Total congenital malformations.*

Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Agerola	7	9.53	94	46.0	2.04	0.0001
2	Massa di Somma	10	5.82	134	86.9	1.54	0.0011

Cluster n.	Municipalities included (number of cases)
1	Agerola (5), Pimonte (6), Gragnano (9), Casola di Napoli (3), Lettere (4), Castellammare di Stabia (52), S. Antonio Abate (15)
2	Massa di Somma (1), San Sebastiano al Vesuvio (7), Pollena Trocchia (8), Cercola (11), Sant'Anastasia (8), S. Giorgio a Cremano (14), Volla (15), Ercolano (29), Portici (25), Somma Vesuviana (16)

Fig. 8 | *Cardiovascular congenital malformations.*

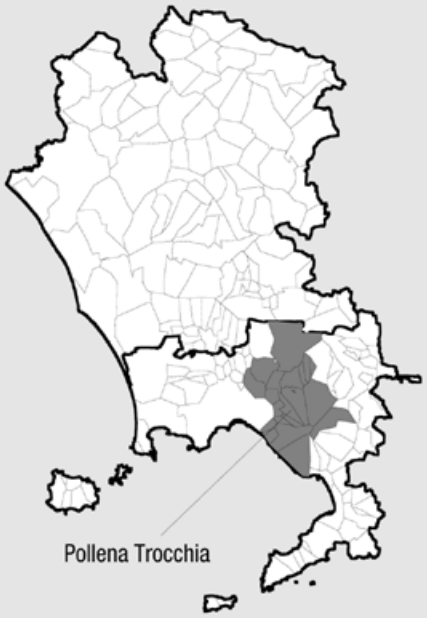
miological surveillance in polluted sites [20, 21]. A commonly adopted indicator of the quality of mortality data is the proportion of ill-defined causes on total deaths: this indicator, in the study area and time window, was 3% in males and 1.4% in females in the Province of Naples; the corresponding figures in the Province of Caserta were 1.6% and 1.2% respectively. These data are in good agreement with the regional average, and they point to a fair quality of death certification.

As far as malformations are concerned, the Campania Register of Congenital Defects covers about 75% of the births occurring in the Region [22]. The Register does not have access to about 45% of births occurring in private hospitals, that are mainly concentrated in the area located around the border of

Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	S. Maria a Vico	6	7.69	7.2	31	4.29	0.0001
2	Acerra	1	-	22	5.9	3.72	0.0002
3	Casaluce	7	2.87	26	11.0	2.38	0.0231

Cluster n.	Municipalities included (number of cases)
1	S. Maria a Vico (4), S. Felice a Cancello (6), Arienzo (1), Cervino (0), Valle di Maddaloni (1), Maddaloni (19)
2	Acerra (22)
3	Casaluce (3), Teverola (2), Frignano (0), Carinaro (2), San Marcellino (5), Villa di Briano (2), Aversa (12)

Fig. 9 | *Urogenital tract congenital malformations.*



Cluster n.	Centroid	Municipalities included	Radius (km)	Observed cases	Expected cases	RR	p value
1	Pollena Trocchia	20	9.98	160	121.2	1.30	0.0218

Cluster n.	Municipalities included (number of cases)
1	Pollena Trocchia (1), Massa di Somma (0), San Sebastiano al Vesuvio (0), Cercola (3), Sant'Anastasia (3), Volla (6), S. Giorgio a Cremano (3), Somma Vesuviana (9), Portici (12), Ercolano (17), Pomigliano d'arco (8), Casalnuovo di Napoli (15), Castello di Cisterna (1), Torre del Greco (28), Ottaviano (5), Brusciano (2), Casoria (16), Afragola (18), Mariglianella (2), Acerra (11)

Fig. 10 | *Limb congenital malformations.*

Naples and Caserta Provinces. This differential proportion of compliance with the Register's requirements observed in the territory of Campania Region might result in under-reporting of congenital malformations in the area were the majority of illegal dumping sites are located.

The results may have been influenced by the size of the population of the municipalities at study and by discontinuity between municipalities. Indeed, single municipalities are more likely picked up in cluster analysis when they are large enough and/or when their estimators (for mortality or CMs) depart substantially from neighbouring values. When two or more municipalities presenting slightly enhanced val-

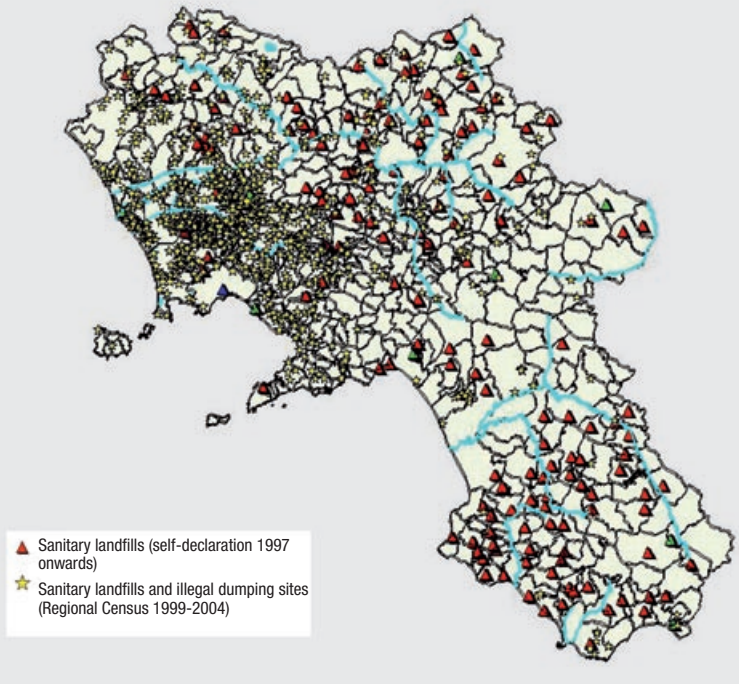


Fig. 11 | *Waste dumping sites geographic distribution in the Campania Region.*

Table 1 | *Congenital malformations and corresponding ICD codes*

Abnormalities	ICD-IX codes	ICD-X codes
Nervous system	740, 741, 7420-7425, 7428, 7429	Q00-Q07
Defects of neural tube	740, 741, 7420	Q00, Q01, Q05, Q070
Congenital cardiovascular diseases	7450-7459, 7460-7469, 7470-7474	Q20-Q26
Palatine vault and lips	7490-7492	Q35-Q37
Digestive tract	7503-7504, 7507-7519	Q39, Q402, Q403, Q408, Q409, Q41-Q45
External urogenital apparatus	7524-7528	Q515, Q516, Q52-Q56, Q640
Hypospady	75260	Q54-Q54.3, Q54.8-Q54.9
Internal urogenital apparatus	7520-7523, 7529-7539	Q50, Q510-Q514, Q517-Q519, Q60-Q63, Q641-Q649
Skeleton, muscles and connective tissue	7444-7445, 7448-7449, 7480-7481 7501-7502, 7540-7542, 7548,	Q18, Q30, Q380, Q382-Q389, Q67, Q680, Q688, Q75-Q79,
	7560-7569, 5240, 5249	Q8704, Q8705, Q8708, Q870A, K070, K079
Limb	7543-7547, 7550-7556, 7558-7559	Q650-Q656, Q66, Q682-Q685, Q69-Q74
Chromosomial	7580-7583, 7585-7589	Q90-Q94, Q96-Q99

ues have common borders, the tendency to clusterize becomes higher. For a more detailed discussion on this topic see Kuldorff [19].

Another limitation may be due to the use of the geographic coordinates of the municipality town hall rather than a centroid based on actual population distribution.

The validity of the adopted study design, on the other hand, is enhanced by the adjustment for socioeconomic deprivation. Its effectiveness in removing confounding has been documented [23]. In any case, it is possible that residual confounding, not captured by the deprivation index, may be present.

Clusters of municipalities with significant excesses of lung, liver, gastric, kidney and bladder cancer have been mainly reported in the southern part of Caserta Province and in the northern part of Naples Province. This subarea largely overlaps with the area were most illegal waste disposal practices, namely dumping of toxic waste and illegal burning of both toxic and solid urban waste took place *(Figure 11)*. This overlapping is particularly evident for the urogenital tract CMs and for kidney, bladder, gastric and lung cancer (in the latter case, excluding the Vesuvian cluster). These neoplastic diseases obviously have a complex multifactorial etiology, but for all of them associations with residence in the neighbourhood of waste disposal sites have been reported [24-30]. With respect to time-related variables, the present study requires a specific comment. When dealing with illegal waste management procedures, dating the onset of exposure and thus latency times can be problematic. In this case, available evidence mainly deriving from criminal trials [7] suggests that illegal practices were operating in the area at least since the '80s. The present study may thus be not fully informative for diseases having a median latency time of more than twenty years.

No cluster of soft-tissue sarcoma and Non-Hodgkin's lymphoma were detected in the present study. Soft-tissue sarcomas are a heterogeneous group of rare diseases, whose diagnosis is quite complex and rapidly evolving [31, 32]. The ICD follows a topographic approach and it groups sarcomas and carcinomas of the same organ under the same code, while the ICD code 171 (malignant neoplasms of soft tissue) does not include visceral, breast and skin cancer, and it is furthermore affected by misclassification due to secondary lesions [33]. Mortality data are thus not suitable for soft tissue sarcoma epidemiology. Also for Non-Hodgkin's lymphoma, international working groups recommend to rely on incidence, rather than mortality data [34]. Notwithstanding these limitations, Non-Hodgkin's lymphoma mortality figures have been extensively used in epidemiological surveillance of populations resident in the surroundings of incinerators [35-37]. Also soft-tissue sarcoma mortality has been investigated in these context [35], with caution expressed by the authors because of the aforementioned methodologic constraints. As mentioned in the Methods section, the rationale to include these ICD codes in the study was based on the necessity to exclude major departures of observed from expected figures.

Also the main clusters of total CMs, cardiovascular, urogenital and limb malformations were prevalently detected in the area across the two Provinces and in large portions of the Province of Naples, mostly interested by illegal waste management.

Increased risks of CMs related to the potential role of exposure to waste pollution is reported and discussed by several epidemiological studies [1, 3, 38-40]. Lumping CMs with different multifactorial etiology produce larger although heterogeneous groups. Despite a greater statistical power, main drawbacks are a lower specificity and a dilution effect that may hide risks acting on specific CMs.

CONCLUSIONS

In conclusion, the present study has detected a tendency towards clustering of several cancer sites and CMs (namely, urogenital malformations) in a fairly well defined area encompassing the northern part of Naples and the southern part of Caserta Provinces. These results have been adjusted for the possible confounding effect of socioeconomic deprivation.

The area identified in this study for hosting most observed clusters:

a) is the same indicated by the previous study for showing peculiar SMR and BMR values, with respect the whole Region;
b) corresponds to the part of Campania Region where most of the illegal practices of dumping toxic wastes took place over time.

The adopted study design was not aimed at evaluating cause-effect relationships, since it does not take into account the different possible risk factors, like smoking, life style, occupation, but rather at pursuing a better knowledge of the spatial distribution of the diseases of interest in an area in which a long-lasting practice of illegal waste management had taken place. This approach represents a step in the construction of an epidemiological framework, consistently with the indications provided by several authors [41, 42], who recommend the implementation of studies both at individual and at population level. Causal relations will then be evaluated integrating epidemiological, clinical and toxicological sources of evidence. It is intended that the scientific background for these evaluation should be coherent with the conclusions of the aforementioned WHO Report [6], according to which there is some evidence of an adverse health effect of residence near waste dumping sites, but a causal link has not yet been ascertained.

Environmental monitoring and epidemiological surveillance will continue in the area, where priorities for environmental reclamation and health investigations can now be selected with more confidence.

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